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10/598,698	09/08/2006	Klaus Hellerbrand	79650-341358	9077

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EXAMINER	
HEYER, DENNIS	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
11/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,698	HELLERBRAND ET AL.	
	Examiner	Art Unit	
	DENNIS HEYER	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 6, 8 – 9, 11 – 17, 48 and 51 – 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, 8 – 9, 11 – 17, 48 and 51 – 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of Applicant's remarks and amendments in the response filed August 13, 2009. Acknowledgement is made of the amendments to Claims 1, 11 and 48. Acknowledgement is made of the cancellation of Claims 2 – 3, 5, 7, 10, 18 – 47 and 49 – 50 and the addition of new claims 51 – 53 in the response filed August 13, 2009. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of Claims

Claims 1, 4, 6, 8 – 9, 11 – 17, 48 and 51 – 53 are currently pending.

Withdrawn Rejections

Claim rejections – 35 USC § 112 – 2nd Paragraph

The rejection of Claim 3 under 35 U.S.C 112 2nd paragraph as indefinite is rendered moot and is withdrawn in response to the cancellation of Claim 3.

Claim rejections – 35 USC § 112 – 1st Paragraph

The Scope of Enablement rejection of Claim 3 under 35 U.S.C 112 1st paragraph is rendered moot and is withdrawn in response to the cancellation of Claim 3.

Claim rejections – 35 USC § 101

The rejection of Claim 48, as being under 35 U.S.C. 101 as being drawn to nonstatutory subject matter is rendered moot and is withdrawn in response to Applicant's amendments.

Claim rejections – 35 USC § 102

The rejection Claims 1 – 5 and 8, 12, 14 and 16 – 17 under 35 U.S.C. 102(e) as being anticipated by Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) is rendered moot and is withdrawn in response to Applicant's amendments.

Claim rejections – 35 USC § 103

The rejection of Claims 1 – 5 and 8, 11 – 12, 14 and 16 – 18 under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) in view of www.science.unitn.it/~gcsmfo/facilities/dip-coating.htm (the 'dip coating method reference', published: October 22, 2004) is rendered moot and is withdrawn in response to Applicant's amendments.

The rejection of Claims 1 – 14, 16 – 18 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) and the 'dip coating method reference' (published: October 22, 2004) as applied to Claims 1 – 5 and 8, 11 - 12, 14 and 16 – 17 above, and further in view of Kohnert *et al.* in WO 2003/043673 (publication date: May 30, 2003) is rendered moot and is withdrawn in response to Applicant's amendments.

The rejection of Claim 15 under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005), the 'dip coating method reference' (published: October 22, 2004) and Kohnert *et al.* in WO 2003/043673 (publication date: May 30, 2003) as applied to Claims 1 – 14, 16 – 18 and 48 above, and further in view of Lee *et al.* in US patent 5,571,523; published November 5, 1996) is rendered moot and is withdrawn in response to Applicant's amendments.

Response to Arguments

Applicant's arguments filed October 13, 2009 with respect to the rejections under 35 U.S.C 102(e) and 35 U.S.C 103(a) have been fully considered and, in light of the amendments to Claims 1 and 11 are rendered moot. Accordingly, a new ground of rejection, necessitated by Applicant's amendments to Claims 1 and 11, are presented below.

New Rejections

Claim rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Instant Claims 1, 4, 6, 8, 11 – 12 and 16 – 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) in view of Klokkers-Bethke *et al.* in US patent 5,335,769 (published: August 9, 1994).

Song teaches a medical device comprising a substrate, a therapeutic agent containing region over the substrate which comprises a therapeutic agent an antioxidant (a coating) as well as methods of making said coated devices (Abstract)

Regarding instant Claim 1, Song teaches providing a solution comprising a solvent, a therapeutic agent and an antioxidant, contacting the solution with a medical device substrate and then removing the solvent from the solution to form a therapeutic-agent-containing region (Abstract). Song teaches 'dipping techniques' (equivalent to inserting the device into the solution) as a preferred solvent-based technique for contacting the device with a solution (instant Claim 1, step c)

Regarding instant Claim 4, the reference teaches that the solution contacting the medical device substrate comprises a therapeutic agent (a therapeutic substance; Abstract).

Regarding instant Claim 6, drawn to immobilization of the pharmaceutically active substance to an inorganic or organic bioresorbable material, Song teaches that the process of contacting the substrate (the previously formed polymer layer) with a solution containing a therapeutic agent (pharmaceutically active substance) results in said agent being "imbibed by the polymer". One of ordinary skill would reasonably construe the process of "imbibing" (defined as: to take in, absorb) to meet the limitation of 'immobilized' as defined in paragraph [0053] of the instant specification. Song also teaches that the imbibing (immobilization) may occur within a bioresorbable material including polypeptide biopolymers coatings (paragraph [0039]).

Regarding instant Claim 8, the reference teaches that the solution contacting the medical device comprises non-active ingredients, specifically, a polystyrene-polyisobutylene block copolymer (page 13, Example 3, paragraph [0050]).

Regarding instant Claim 12, the solution contacting the medical device is an organic solvent, tetrahydrofuran (page 13, Example 3, paragraph [0050]).

Regarding instant Claim 14, wherein the solution contacting the medical device contains an antioxidant, the reference teaches that the solution contacting the medical device may comprise an antioxidant, such as BHT, BHA or tocopherol (Abstract, step a (iii), paragraph [0009], see also, page 13, Example, paragraph [0050]).

Regarding instant Claims 16 and 17, the reference teaches that the medical device may be a stent (page 13, Example 3, paragraph [0050]) and that the medical device includes any coated substrate which can comprise, for example, metal (page 3 – 4, paragraph [0020].

Instant Claim 1, step (d) recites the newly amended limitation that the device is coated by “starting isothermal drying of the device while the device remains held within the solution held within the container, thereby removing the volatile components from the solution of the coating substance". One of ordinary skill would readily recognize that, in light of Applicant's definition of isothermal drying (defined on page 20, lines 7 – 25 of the instant specification to include freeze-drying and vacuum-drying) that step (d) reads on the well-known process of lyophilization.

Song does not teach expressly teach the process of isothermal drying as recited in instant Claim 1, step (d), or the limitation of instant Claim 11, wherein the container from which the solvent is removed becomes the packaging container for the device.

Klokkers-Bethke *et al.* teach a method for packaging lyophilizates in glass containers that become the packaging container (the “primary packaging means”,

column 1, lines 9 – 10). Klokkers-Bethke teaches that moisture sensitive medicinal substances must be stabilized for storage and that a customary stabilizing method is to dry a solution of said substance by removing the solvent by lyophilization (column 1 , lines 17 – 21). Klokkers-Bethke teaches lyophilization (isothermal drying) of a therapeutic substance, prostaglandin-E1 (PGE1), using as a primary packaging means, a glass container (column 3, lines 33 – 35). Stated otherwise, Klokkers-Bethke teaches lyophilization of a therapeutic agent by starting isothermal drying in which a therapeutic substance, PGE1, remains within the solution held within a glass container that becomes the packaging container (instant Claims 1, step (d) and 11). Klokkers-Bethke teaches that freeze drying followed by sealing the container (the packaging container) "maintains the product stable over a useful storage shelf life" (column 3, lines 18 – 22).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to adapt the method of Song to prepare a medical device coated with a therapeutic agent and an antioxidant with the lyophilization procedure of Klokkers-Bethke (i.e. within the "primary packaging container) in order to provide a stable moisture free environment and thus extend the product shelf life. Further, one would have been motivated to carry out the lyophilization step (step (d))as taught by Klokkers-Bethke because Song teaches that it may be beneficial to maintain a therapeutic agent coated onto a medical device in a non-oxidizing environment during the course of its formation (page 12, paragraph [0046] and [0047]) and, that subsequent to it's formation, it may be beneficial to place the coated medical device into packaging that has been evacuated or into which an inert gas has been introduced in order to

maintain a non-oxidizing environment (paragraph [0047]). One of ordinary skill would recognize that the lyophilization (isothermal drying) method of Klokkers-Behtke teaches extending the shelf life of a therapeutic agent by providing the inert (oxygen-free and thus anti-oxidizing) environment taught by Song.

Instant Claims 9, 13, 48 and 52 – 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) in view of Klokkers-Bethke et al in US patent 5,335,769 (published: August 9, 1994), as applied to Claims 1 – 5 and 8, 11 – 12, 14 and 16 – 17 above, and further in view of Kohnert *et al.* in WO 2003/043673 (publication date: May 30, 2003).

As noted in the103(a) rejection above, Song in combination with Klokkers-Bethke reference teach the method recited in instant Claims 1 – 5 and 8, 11 – 12, 14 and 16 – 17.

The Song reference does not teach a coating substance comprising calcium phosphates (instant Claim 9), or the device being calcium phosphate or β-tricalcium phosphate (instant Claims 52 – 53). The Song reference also does not teach an acidic aqueous contacting solution (instant Claim 13), or that the method of instant Claim 1 provides a homogeneous distribution of the coating on the device (instant Claim 48).

Kohnert teaches devices having osteoconductive and osteoinductive properties (Title) comprising a carrier containing calcium phosphate wherein said carrier is homogeneously coated with protein (Abstract). Kohnert teaches a method for preparing

said devices comprising providing a solution comprising an osteoinductive protein and a buffer and contacting the solution with a carrier containing calcium phosphate.

Regarding instant Claim 9, Kohnert teaches that the contacting solution comprises a carrier containing calcium phosphate (page 6, 3rd paragraph). Kohnert teaches that the device may be made of calcium phosphate or β-tricalcium phosphate (Claim 11, instant Claims 52 and 53).

Regarding instant Claim 13, Kohnert teaches that the contacting solution comprises a buffer, and that, preferably, the preferred pH is between 4 and 6 (page 8, paragraphs 3 and 4), which meets the limitation of the instant Claim that the contacting solution be an aqueous acidic solution.

Regarding instant Claim 48, drawn to a homogeneous distribution of the coating on the device, Kohnert teaches a method that provides a homogeneous coating on the surface of the device (page 6, paragraph 3 to page 7 paragraph 1, in particular step (c)) and teaches that an advantage of the present invention is the homogeneous coating which is achieved during the coating process (page 7, paragraph 4).

The motivation to apply the method of coating a device as taught by Song and Klokkers-Bethke, to an acid aqueous solution (preferably pH 4 - 6) is provided by Kohnert who teaches that said pH ranges prevent the precipitation of the bone morphogenic member protein (BMP) family member, GDF-5, from solution and insures the device achieves a homogeneous coating (page 7, paragraph 3 and 4) as nonhomogeneous coatings can lead to decreased osteoinductive properties (page 6, 2nd paragraph). Therefore, Kohnert provides specific motivation to optimize the nature

of the coating solution (from an organic solvent to an aqueous acidic solution at pH 4 – 6) of Song by teaching that the protein-derived therapeutic agents taught by Song, which include BMP protein (Song, paragraph [0033]), will remain in solution at an aqueous solution at pH 4 – 6.

One would have been motivated to combine a bioresorbable material such as calcium phosphate and β-tricalcium phosphate with the method of Song and Klokkers-Bethke because Kohnert teaches that said materials are effective bone-replacement materials (page 1, paragraph 2) and thus are art-recognized as components of medical devices.

Thus it would have been *prima facie* obvious to one of ordinary skill in the art, to apply the method of Song and Klokkers-Bethke with the teachings of Kohnert, at the time the invention was made, to arrive at the claimed invention with a predictable and reasonable expectation of success.

Instant Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) and Klokkers-Bethke *et al.* in US patent 5,335,769 (published: August 9, 1994), as applied to Claims 1 – 5 and 8, 11 – 12, 14 and 16 – 17 above, and further in view of Lee *et al.* in US patent 5,571,523; published November 5, 1996)

As noted in the 103(a) rejections above, the Song in combination with Klokkers-Bethke teach the method of instant Claim 1. Song teaches that the solution contacting

the medical device comprises an antioxidant (such as BHT, BHA or tocopherol, instant Claim 14), but does not expressly teach methionine as the antioxidant.

Regarding instant Claim 15, Lee *et al.* teach a method for inhibiting arteriosclerosis by contacting an artery with an apoptosis-inducing amount of an antioxidant (Abstract) in which methionine is a preferred antioxidant (column 1, lines 37 – 43, Claim 7). Lee teaches that one means for locally delivering the antioxidant is by providing (coating) the antioxidant on the surface of a vascular catheter (a medical device) which contact the wall of a blood vessel (column 1, lines 64 – 67). Thus, it would have been *prima facie* obvious to one skilled in the art, at the time the invention was made, to adapt the method of Song and Klokkers-Bethke and use methionine as an antioxidant in place of tocopherol, BHA or BHT on a coated medical device, such as a stent or catheter. One would have been motivated to do so because methionine is effective at inhibiting arteriosclerosis and has been taught by Lee that a means of delivering methionine to a blood vessel is via an implantable medical device.

Instant Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Song in WO 2005/016399 A1 (filing date: August 11, 2004, published: February 24, 2005) and Klokkers-Bethke *et al.* in US patent 5,335,769 (published: August 9, 1994), as applied to Claims 1 – 5 and 8, 11 – 12, 14 and 16 – 17 above, and further in view of Gao *et al.* in US patent 6,113,993 (published: September 5, 2000).

As noted in the 103(a) rejection above, Song in combination with Klokkers-Bethke teach the method of instant Claim 1. Song teaches a method for coating a wide

range of implantable medical devices in which the coated substrate can comprise metal (paragraph [0020]) but does not expressly teach a device made of titanium or a titanium alloy as recited in instant Claim 51.

Gao teaches a method of coating an implant with a calcium phosphate compound on a titanium substrate (Abstract). Gao teaches that orthopaedic implants are commonly made of titanium alloy because of its corrosion resistance to body fluids. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to apply the method of coating a medical device taught by Song and Klokkers-Bethke to a device made of titanium. One would have been motivated to do so because implants are commonly made of titanium alloys to gain the benefit of their corrosion resistance to body fluids.

Conclusion

Claims 1, 4, 6, 8 – 9, 11 – 17, 48 and 51 – 53 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DENNIS HEYER whose telephone number is (571)270-7677. The examiner can normally be reached on Monday-Thursday 8AM-5PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, BRANDON FETTEROLF can be reached at (571)272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DH

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642